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COVID Impacts: Immune Dysfunction

Detailed information and resources on the long-term health consequences of COVID-19 infection and the broad social impacts of the COVID-19 pandemic

COVID-19 Immune Dysfunction

One of the most concerning long-term impacts of COVID-19 is immune dysregulation and dysfunction. Immune system impacts were heavily documented, even in the first waves of the pandemic, however there was a lack of understanding as to what exactly COVID-19 infections were doing to the immune system, and what that might mean both during acute infection and long-term.

Early Hypotheses

Early on in the pandemic, there were two main hypotheses for the pathophysiology of COVID-19 severe disease and death: hyperactive immune system and immune system failure.

Hyperactive Immune System

The first was due to an overactive immune system. Early on it was noted that many patients with severe COVID-19 ended up developing ARDS (acute respiratory distress syndrome). This was reminiscent of the cytokine release syndrome (CRS) - induced ARDS and secondary hemophagocytic lymphohistiocytosis (sHLH) that had been observed previously in patients with SARS-CoV and MERS-CoV (it also is a common adverse event in cancer patients treated with CAR-T cell therapies).

Therefore it lead researchers to believe that severe infections were the results of an overactive immune response caused by excessive inflammatory cytokines, which lead to inflammatory lung and vascular injuries, and that death was from subsequent respiratory failure or coagulopathy.

Immune System Failure

The second hypothesis took the exact opposite hypothesis, that COVID-19 caused immune collapse. In this hypothesis, COVID-19 causes the patient's protective immunity to collapse, causing uncontrolled viral replication and dissemination which lead to cytotoxicity and death. Support for this contrasting theory was based on the observed progressive and profound lymphopenia, often to levels seen in patients with AIDS.

More recent research has concluded that COVID-19 causes dysregulation to both the innate and the adaptive immune systems. Paradoxically, in COVID-19 pneumonia, the innate

New-Onset Autoimmune Diseases

What are Autoimmune Diseases?

A healthy immune system defends the body against disease and infection. But if the immune system malfunctions, it mistakenly attacks healthy cells, tissues, and organs. Called autoimmune disease, these attacks can affect any part of the body, weakening bodily function and even turning life-threatening.

Scientists have identified more than 80 autoimmune diseases. Some are well known, such as type 1 diabetes, multiple sclerosis, lupus, and rheumatoid arthritis, while others are rare and difficult to diagnose. Oftentimes with autoimmune diseases, especially rare diseases, it can take years of suffering before getting a proper diagnosis. An estimated 24 million Americans suffer from autoimmune diseases, with an additional eight million carrying the "autoantibodies" that predispose individuals to develop autoimmune diseases.

It has long been documented that infections, especially viral infections can trigger autoimmunity and autoimmune diseases, especially in those who carry genetic risk factors (autoantibodies) for such diseases.

Epstein-Barr Virus (EBV) has long been associated with the ability to hide in host cells and switch between active and latent infection. EBV is a herpes virus that can cause infectious mononucleosis. It can live in the body indefinitely and even in its latent (inactive) state can cause diseases later in life, including multiple cancers, systemic autoimmune diseases, and multiple sclerosis.

COVID-19 Associated Autoimmunity

COVID-19 has been reported to present immunological features that resemble those of autoimmune diseases, such as over-activation of mature natural killer cells, $CD8^+$ T cells, and dysregulation of B cells and T cells. Also, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may lead to dysregulation of immune response and increased inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6.

There have already been many documented cases of autoimmune disease following COVID-19 infections,

immune system fails to mount an effective antiviral response while also inducing potentially damaging inflammation.

Acute COVID-19 Infection & Immune Dysregulation

In the early days of the pandemic, it was well documented that patients with severe COVID-19 infections had pronounced immune dysregulation with lymphopenia and increased expression of inflammatory mediators.

COVID-19 Alters Both Innate and Adaptive Immunity

The immune system is made up of two parts: the innate (general) immune system and the adaptive (specialized) immune system. These two systems work closely together and take on different tasks.

Patients with severe acute COVID-19 infection exhibit increased T-cell activation and subsequent T-cell exhaustion. This T-cell reduction of functional T-cells was pronounced and sustained beyond the acute infection. Early research found that in non-hospitalized COVID-19 patients, these immune cells returned to baseline fairly quickly but were sustained in those with severe COVID-19 infection.

Severe COVID cases were found to have decreased production of early immune responses (INF) which in turn lead to the virus replicating and causing severe cellular lung damage. Not only was the antiviral response of IFN delayed and reduced, but it was also accompanied by an overexaggerated inflammatory response with excessive cytokines. This resulting hyperinflammation caused edema, fibrosis, and thromboses in the lungs that ultimately lead to hypoxia, acute respiratory distress syndrome (ARDS) and death.

Innate Immunity

Responsible for the initial immune response and antiviral activity, the innate system functions as a single defense mechanism, crucial for host response and illness protection.

Now, three years into the pandemic, with millions of infections and immunizations behind us, severe acute COVID-19 infections are becoming significantly less common, though COVID-19 is still causing significant hospitalizations and mortality across the globe. But generally speaking most individuals are no longer concerned with the acute infection stage of COVID-19. To the point that getting the virus may seem unremarkable and not a cause for concern.

Adaptive Immunity

The adaptive immune system is critical for the development of efficient host responses to invading pathogens as well as immunological memory for future infections of similar pathogens.

Although COVID-19 patients may exhibit elevated levels of inflammatory cytokines compared to non-critically-ill patients, a study comparing the immune profiles of COVID-19 and influenza noted that while a 3–4% subset of COVID-19 patients exhibited hyperinflammation characteristic of a cytokine storm, they more commonly demonstrated immunosuppression.

CD4+ helper T cells and CD8+ cytotoxic T cells have been identified as crucial in the immunologic response to SARS-CoV-2 infection. $CD4^+$ T cells are responsive to the virus's spike protein, and the presence of $CD8^+$ T cell expansion in bronchoalveolar lavage is correlated with illness moderation. However, one of the most remarkable characteristics of

Long-Term COVID-19 Immune Dysfunction

However, a new idea about how COVID can affect immunity has emerged: that even mild infections routinely cause consequential damage to our bodies' defenses. This degradation was referred to as "immunity theft" by T. Ryan Gregory, an evolutionary biologist, as a counterargument to "immunity debt" being the reason why respiratory infections were more severe than usual this past fall.

So while the acute infection may be one reason to not want to keep getting infected with SARS-CoV-2 over and over again, the idea that it can increasingly cause damage to the immune system should be a significant reason. Throughout the pandemic, scientific evidence has mounted that even mild COVID infections may be doing something to our immune systems, as well as our collective immunity.

For example, what if SARS-CoV-2 infection causes the immune system to be able to respond to SARS-CoV-2 in such a way that we no longer experience severe COVID infections, but rather it causes a subtler, long-term immunological

Long-Term Immune Damage

A retrospective cohort study published in February 2023 in the journal *Clinical Medicine* found that those who had documented COVID-19 infection had significantly higher risks of the following autoimmune diseases compared those without COVID-19:

- Rheumatoid arthritis
- Ankylosing spondylitis
- Systemic lupus erythematosus
- Dermatopolymyositis
- Systemic sclerosis
- Sjogren's syndrome
- Mixed connective tissue disease
- Behçet's disease
- Polymyalgia rheumatica
- Vasculitis
- Psoriasis
- Inflammatory bowel disease
- Celiac disease
- Type 1 diabetes

Viral Reactivation

Most human viruses have one phase of viral replication, the lytic phase. The viral genome is packaged into a viral coat and released from the cell. This process of viral release from the cells results in lysis of cells, and hence the 'lytic phase'.

However, there are a handful of human viruses that have another phase of replication, usually referred to as the 'latent phase', in other words the virus lays dormant in the host cell. This latent phase of replication / latent infections have the ability to be reactivated into lytic form. The ability to move backand-forth from latent to lytic infections helps the virus spread from infected individuals to uninfected individuals.

Reactivation is the mechanism whereby a latent virus that has infected a host cell switches to a lytic stage, undergoing productive viral replication and allowing the virus to spread. Viral reactivation is associated with several stress factors, including viral infection (with other viruses including SARS-CoV-2), nerve trauma, physiologic and physical changes (e.g., fever, menstruation and exposure to sunlight) and immunosuppression.

Patients with severe COVID-19 have been characterized by impaired immunity, hyperinflammation, lymphopenia, and cytokine storms, all of which can lead to severe immunosuppression and immune dysfunction.

- Viral reactivations and co-infections in COVID-19 patients: a systematic review

  Kim JYH, Ragusa M, Tortosa F, et al. Viral reactivations and co-infections in COVID-19 patients: a systematic review. BMC Infect Dis. 2023;23(1):259. Published 2023 Apr 26.

- Chronic viral coinfections differentially affect the likelihood of developing long COVID

  Peluso MJ, Deveau TM, Munter SE, et al. Chronic viral coinfections differentially affect the likelihood of developing long COVID. J Clin Invest. 2023;133(3):e163669. Published 2023 Feb 1.

- Persistent SARS-CoV-2 Infection, EBV, HHV-6 and Other Factors May Contribute to Inflammation and Autoimmunity in Long COVID

  Vojdani A, Vojdani E, Saidara E, Maes M. Persistent SARS-CoV-2 Infection, EBV, HHV-6 and Other Factors May Contribute to Inflammation and Autoimmunity in Long COVID. Viruses. 2023;15(2):400. Published 2023 Jan 31.

changes that leave us more vulnerable to *other* infections or even chronic disease?

COVID-19 Impacts Immune System Response & Vaccination

A March 2023 study published in the journal Immunity looked at how the immune system responds to both COVID-19 infection and COVID-19 vaccination. What the researchers found was that the magnitude and quality of $CD8^+$ T cell activation and expansion after two COVID-19 vaccine doses were considerably lower in people with prior SARS-CoV-2 infection compared to people without prior infection, suggesting that previous infection can influence the T cell response to vaccination.

Taken together, the researchers write, "these findings suggest that SARS-CoV-2 infection damages the CD8+ T cell response, an effect akin to that observed in earlier studies showing long-term damage to the immune system after infection with viruses such as hepatitis C or HIV. The new findings highlight the need to develop vaccination strategies to specifically boost antiviral CD8+ T cell responses in people previously infected with SARS-CoV-2, the researchers conclude."

- Immune mechanisms underlying COVID-19 pathology and post-acute sequelae of SARS-CoV-2 infection (PASC)
  Mohandas S, Jagannathan P, Henrich TJ, et al. Immune mechanisms underlying COVID-19 pathology and post-acute sequelae of SARS-CoV-2 infection (PASC). Elife. 2023;12:e86014. Published 2023 May 26.
- Post-acute sequelae of COVID-19 is characterized by diminished peripheral CD8+β7 integrin+ T cells and anti-SARS-CoV-2 IgA response
  Santa Cruz A, Mendes-Frias A, Azevedo R, et al. Post-acute sequelae of COVID-19 is characterized by diminished peripheral CD8+β7 integrin+ T cells and anti-SARS-CoV-2 IgA response. Nat Commun. 2023;14(1):1772. Published 2023 Mar 30.